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Review

Stem cells are the foundation for every organ and tissue in our body. They are of 4 types, Embryonic stem cells obtained from the inner cell mass of the blastocyst, tissue-specific stem cells, mesenchymal stem cells derived from stroma, induced pluripotent stem cells. Adult stem cells can be obtained from different sources, like bone marrow, adipose tissue, or post-natal tissues such as umbilical cords and placenta. Mesenchymal stem cells have therapeutic potential for treating immune mediated and neoplastic human diseases. However, the difficulty of isolating adult stem cells from different tissues due to the invasiveness of the extraction methods and the need for *in vitro* expansion are limiting factors in their clinical use. Menstrual-derived stem cells are a highly proliferative stem cell population that is able to differentiate under standard laboratory conditions into specific-tissue cells of all the three germ layers [1].

It was shown that adherent cells derived from the endometrium are capable of differentiating into 9 lineages, namely, cardiomyocytic, respiratory epithelial, neurocytic, myocytic, endothelial, pancreatic, hepatic, adipocytic, and osteogenic cells [1,2]. Menstrual stem cells expand rapidly and maintain greater than 50 percent of their telomerase activity when compared to human embryonic stem cells and are considered better than bone marrow-derived stem cells. However, we still need more information on their immunomodulatory and diagnostic properties, and also about how epidemiological factors, such as age, use of contraceptives, or hormonal status can affect their therapeutic potential, to properly assess their current and future use in clinical application and diagnosis.

Review Article

Menstrual Stem cells

Abstract

Stem cells isolated from menstrual fluid have mesenchymal stem cell like properties and have multi-lineage differentiation capacity. Menstrual fluid has ease of access in collection and repeated sampling is possible in a noninvasive manner. Also, rapid culture of these is possible in numbers that are sufficient for therapeutic use. They are, hence, looked upon as a novel innovation and are finding a place in the current medicine practice.

It was shown that menstrual stem cells from the menstrual fluid of young healthy women grew fast, doubling every 19.4 h, which is twice faster than bone marrow-derived mesenchymal stem cells, estimated at 40–45 h in early passages [1]. A good proliferation rate is essential for clinical applications since cell-based therapies are dose dependent, preferably with cells from lower passages.

How to collect sample

The menstrual blood is collected in a physician's office using a medical-grade silicone cup in place of a tampon or sanitary napkin. The menstrual stem cells are stored in two cryovials that are overwrapped to safeguard them during storage. The overwrapped vials are cryogenically preserved in a facility that is closely monitored at all times to ensure that these menstrual stem cells are safe and ready for future use.

Advantages

1. Mesenchymal stem cells are more easily accessible and have a non-invasive isolation procedure when compared with bone marrow stem cells and cord stem cells.
2. Mesenchymal stem cells (from menstrual blood) have a higher potential to replicate fat, cartilage, bone and skeletal muscle cells.
3. An unlimited number of purified mesenchymal stem cells can be obtained from a single sample. These cells are more proliferative and multiply for longer duration without much damage to DNA. Thus, more cells are available for therapeutic use, even if initial number is small. This ensures that these valuable cells can be used for therapy more than once.
4. Mesenchymal stem cells exert extensive immunomodulatory effects *in vitro* and *in vivo*. These cells inhibit



mixed lymphocyte reaction and promote regulatory T cell generation (Tregs) [3].and also, curb T helper (Th) 1 and Th17 differentiation among other suppressive effects. As they remain hypoimmunogenic or immune privileged, they can be successfully used therapeutically in allogenic or xenogenic conditions.

5. Ease of administration unlike other cell therapies, mesenchymal stem cells can be administered through a standard IV line also. This makes it very convenient for the clinician and the patient.
6. Safety Mesenchymal stem are well tolerated and there have been no reports of toxicity, side effects or fatalities so far.
7. Pain collecting menstrual blood is harmless, painless and quick while bone marrow donation is an invasive and painful procedure.
8. These cells are devoid of ethical dilemmas or medical complications for cell harvesting.
9. These cells display novel properties regarding paracrine effects mediated by secreted factors.

Disadvantages

1. In all the menstrual stem cells studies, cells have been isolated from healthy donors. There are no published reports yet characterizing the property changes if the same are isolated from epidemiologically different background donors or people with pathologies.
2. The effects of age, hormonal status (post-puberty versus pre-menopausal), or prior contraceptive usage remain unknown. As stem cells are sensitive to environmental changes and stress conditions, we can speculate that these variations may affect their function and properties.
3. Antibiotic cover may be required for the sake of sterility of sample.
4. Endometrial stem cells show a lower replicative ability in comparison with adipose tissue-derived mesenchymal stem cells.
5. Expensive
6. Some may feel disturbed regarding the source of these cells. There are certain communities that have stigmas attached with menstruation.

Uses

Heart Failure/Post Myocardial Infarct

The prospect of using mesenchymal stem cells in heart failure uses the ability of these cells to directly differentiate into cardiomyocytes [4] and also to secrete certain angiogenic and trophic factors [5–7]. That assist in regeneration and activation of endogenous cardiac stem cells [8]. Mesenchymal stem cells

appear to be immune privileged and immune modulatory, they are poor stimulators of allogeneic immunity and have been shown to actively inhibit ongoing immune responses in many patients [9,10].

Stroke

The theory for the use of stem cells in stroke says that oxygen glucose deprivation stroke neurons, co-cultured with menstrual blood-derived stem cells or exposed to the media from cultured menstrual blood, exhibited significantly reduced cell death. Transplantation in adult rats after experimentally induced ischemic stroke, intracerebrally or intravenously, significantly reduced behavioral and histological impairments compared to rats with only vehicle infusion.

Others

These stem cells could potentially be used to treat Alzheimer's disease, Lou Gehrig's disease, amyotrophic lateral sclerosis, liver cirrhosis/end stage liver disease [11]. Burns, various skin diseases [12]. Heart disease, osteoarthritis and rheumatoid arthritis, acute lung injury and for the treatment of type 1 diabetes. In vitro and in vivo assessments of transplanting menstrual blood-derived stem cells reveal their efficacy and safety in stroke. They are a potential cell source for treating other CNS disorders [13]. Use in diabetes to prolong graft tissue survival is being considered [14]. Menstrual stem cells-derived exosomes acts as blockers of the tumor-induced angiogenesis and therefore could be suitable for anti-cancer therapies [15].

The autologous stem cell implantation leads to endometrial regeneration reflected by restoration of menstruation and is a promising novel cell based therapy for refractory Asherman's syndrome [16]. Endometrial stem cells have also helped to reveal the pathogenesis of endometriosis and endometrial carcinoma [17].

The other prospective property of menstrual stem cells is their potential as biomarkers that could be highly informative of the risk of asymptomatic early pregnant women subsequently developing complications of pregnancy. Such tests will offer valuable clinical information and will provide an opportunity for early intervention and therapy [18].

They may also be used in men using allogeneic menstrual stem cells.

Comparison of menstrual stem cells and bone marrow stem cells

Menstrual stem cells have higher proliferation rate, colony forming unit frequency, migration capacity, high expression level of mesodermal antigens and multilineage capacities. They also exhibit higher angiogenic effect on endothelial cells both in vitro and in vivo. They are better for hematopoietic cell line differentiation. Their feeder layers display higher clonogenic potential [19].

Multipotent stromal stem cells can also be obtained through



extraction of bone marrow mesenchymal cells. This, however, poses a significant challenge in that the procedure is extremely invasive and limits the use of the cells in research [20].

However, there are hurdles of teratoma formation and the ethical controversies over the creation, usage, and destruction of human embryos. Being totipotent cells, embryonic stem cells can differentiate into many different types of cells and may cause a teratoma if injected directly into a foreign body. The alternative is to explore the application of somatic stem cells and determine if this disadvantage can be thwarted.

Comparison of menstrual stem cells with other stem cells is given in the table below [19], (Table 1)

Conclusion

Menstrual stem cells, till date, have been tested only in very limited disease models. These cells have been shown to possess various regenerative properties, under both, physiological and pathological conditions. Future research and new evidence would greatly contribute to make menstrual stem cells a preferred type of stem cell, for new therapies and novel diagnostic tools.

Table1:

	Embryonic	Bone marrow	Adipose	Dental	Placenta/ Cord	Menstrual blood
Ethical	-	+	+	+	+	+
Immunomodulation	+	+	+	+	+	+
Invasiveness	+	-	-	-+	+	+
Autologous	+	+	+	+	-+	+

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